UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,321	09/03/2002	Ian George Charles	HO-P02379USO	3580

26271 7590 03/23/2005

FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,321	CHARLES ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11-14 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,11-14 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 10 January 2005 in response to the Non-Final Office Action mailed 9 August 2004. Claims 15-25 were withdrawn from consideration and claims 1-7, 11-14 and 26 were considered in the 9 August Office Action. Claims 15-25 were canceled and claims 4, 5 and 26 were amended in the 10 January Paper. Claims 1-7, 11-14 and 26 are presently pending and under consideration.

Formalities

Priority

Applicant's statement regarding filing of a certified copy GB 0016172.9 application with the International Bureau is acknowledged. The Office will request a copy of the application from the IB.

Sequence Compliance

In reply to the request for a statement that the paper copy and CRF filed 21 October 2001 includes no new matter, Applicant asserts that there was no amendment made to the sequence listing. Applicant's attention is directed to Rule 1.821(g), which states:

> If any of the requirements of paragraphs (b) through (f) of this section are not satisfied at the time of filing under 35 U.S.C. 111(a) or at the time of entering the national stage under 35 U.S.C. 371, applicant will be notified and given a period of time within which to comply with such requirements in order to prevent abandonment of the application. Any submission in reply to a requirement under this paragraph must be accompanied by a statement that the submission includes no new matter. (emphasis added)

Thus, any submission of a substitute sequence listing or CRF submitted after the filing of the application must include a statement that the submission includes no new matter. Therefore, the statement filed with the 10 January Paper does not comply with the requirements of 37 CFR 1.821. Applicant is again requested to submit a statement that fully complies with the Rule.

Response to Amendment

Claim Objections

Objection to claims 5 and 26 as containing informalities is withdrawn in view of the amendments thereto.

Claim Rejections - 35 USC § 112

Claims 1-7, 11-14 and 26 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record and herein below in the response to arguments.

Claims 1-7, 11-14 and 26 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record and herein below in the response to arguments.

Rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of the amendment thereto.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 1-7, 11-14 and 26 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claims were rejected on the grounds that the disclosure fails to adequately describe the genus embraced by the functional variant of NOS of the claims, which is understood to be generic to a polynucleotide encoding any polypeptide capable of synthesizing nitric oxide.

In response to the *prima facie* case of record, Applicant urges that the written description requirement does not compel the Applicant to describe exactly the subject matter claimed, instead the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.

While this general principle is acknowledged, as far as it goes, Applicant is reminded, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" ("Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, first paragraph, 'Written Description' Requirement" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966). In other words, one of ordinary skill in the art would not recognize that Applicant was in possession of a product or method of using a product if a critical element, such as the functional variant of NOS, were not adequately described.

While acknowledging that skilled person would understand that the term "functional variant" encompasses the use of any polynucleotide encoding any polypeptide capable of synthesizing nitric oxide, Applicant maintains that the full scope of the genus is supported by a disclosure of how such functional variants might be generated and a disclosure of fragments of human iNOS and nNOS having the function of a NOS protein (fourth full paragraph on page 6). Applicant goes on to argue, "[i]n particular, it would be well within the ordinary skill in the art to determine whether any given polynucleotide encodes a polypeptide which is functional variant of a NOS, for example by expressing such a polypeptide recombinantly and then determining whether it is capable of producing nitric oxide from arginine. It can be seen therefore that those of ordinary skill in the art would know how to determine whether any given variant of a NOS is a functional variant in accordance with the invention" (fifth full paragraph on page 6).

These arguments have been fully considered but are not deemed persuasive. First, Applicant is reminded that the Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (Federal Register, Vol. 66, No. 4, Column 3, page 1106). The disclosure of fragments of human iNOS and nNOS having the function of a NOS protein does not adequately represent a genus that embraces any polypeptide that exhibits the recited function wherein the structure of the polypeptide is unlimited.

Furthermore, Applicant is reminded that *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). An adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for

isolating it; what is required is a description of the nucleic acid itself. It is not sufficient to define a nucleic acid solely by its principal biological property (*i.e.,* encoding any polypeptide capable of synthesizing nitric oxide) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any nucleic acid with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all nucleic acids that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Finally Applicant cites *In re Vaeck* 947 F.2D 488, 496 (FED.C1R.1991) (quoting *In re Angstadt*, 537F.2D 498,502-03 (CCPA 1976)) and contends that it is well settled that patent Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, this argument again confuses the "written description" requirement of 35 USC §112, first paragraph, with enablement for "how to make", which is what is addressed in the passage cited from *In re Vaeck.* The Court in *In re Vaeck* does not consider the "written description" requirement of 35 USC §112 and, therefore, the statements cited by Applicant are not germane to the instant rejection.

Applicant's arguments have been fully considered but are not deemed persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 USC §112, first paragraph, as lacking adequate written description.

Claims 1-7, 11-14 and 26 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The previous Office Action concludes, based on a careful analysis of the claimed subject matter, the instant disclosure and the state of the relevant art, that one of ordinary skill in the art would not be able to use the claimed microcapsules in a method of treating a host suffering from a condition associated with deficient NO production, as asserted in the specification, without undue experimentation. Thus, the specification fails to identify an enabled use for the claimed products. Furthermore, as there is no enabled use for the products, the method of making said microcapsules also lacks an enabled use.

To summarize the conclusions set forth in the previous Office Action, although all of the uses contemplated in the specification are directed to therapeutic application of the encapsulated cells, neither the disclosure nor the relevant art provide a single working example of a therapeutic use for the claimed invention or even a closely related invention. The specification clearly does not disclose the manner and process of using microencapsulated cells comprising a construct in which a NOS is operably linked to an ecdysone- or tetracycline-inducible promoter to treat any condition. The art teaches that the platform technologies upon which the invention is based (*i.e.*, microencapsulated cells, and tetracycline- and ecdysone-inducible promoters) were not enabled for clinical use at the time of filing or well after the time of filing. Given that the specification provides no guidance regarding microencapsulation or inducible promoters beyond what was readily available in the art, the skilled artisan seeking to use the invention as contemplated in the specification would clearly have to engage in undue experimentation to enable the platform technologies.

Furthermore, even if the platform technologies were enabled for clinical use, developing a therapeutically effective strategy to treat any given condition would require undue experimentation. The specification provides no specific guidance at all with regard to how one should administer the encapsulated cells to treat of hyperlipidemia, renal failure, hypertension, restenosis after angioplasty, atherosclerosis and its complications, complications of heart failure or schizophrenia. Given the volatile nature of NO *in vivo* the skilled artisan would expect that the encapsulated cells would have to be administered such that they are in close proximity to the relevant target cell; however, the specification provides no guidance as to what the relevant target cells would be or how to deliver the microcapsules to those particular cells. Furthermore, given the toxicity of NO, the skilled artisan would expect that NO expression would have to be tightly regulated in order to achieve a therapeutic effect without inducing toxicity in the patient or in the engrafted cells.

Likewise, the skilled artisan seeking to treat cancer using the microencapsulated cells would not know how to treat a clinically relevant tumor *in situ* using the invention. The admixture of dispersed tumor cells with dispersed microencapsulated cells as provided in Example 6 clearly fails to model the complexity of a tumor *in situ*, and given the general failure of xenograft tumor models of cancer to predict clinical efficacy of cancer treatments, the clinical outcome of administering the encapsulated cells to a cancer patient is highly unpredictable. Thus, the skilled artisan seeking to use the microencapsulated cells of the invention to treat cancer would clearly have to engage in undue experimentation to establish a clinically efficacious treatment.

In response to the *prima facie* case of record, Applicant submits that each of the assertions set forth in the rejection are rebutted by the information provided in the application or not relevant.

Applicant argues that the fact that the promoters used in the specification may or may not be sanctioned for clinical use is not an issue that is relevant to enablement as the requirements for regulatory approval are wholly separate from those for patentability. While the concept underlying Applicant's comment is valid, it should be made clear that the Office Action does not set forth the absence of regulatory approval as the basis for the enablement rejection. Instead, the Office Action cites teachings that establish the unpredictable nature of the art and the degree of experimentation required to use the invention as contemplated. For example, in the paragraph bridging pages 7-9, the Office Action cites the teachings of Orive *et al.*, which demonstrate the many obstacles to be overcome before encapsulated cells can be used clinically. Likewise, the discussion beginning in the paragraph bridging pages 10-11 and continued through the paragraph bridging pages 11-12 demonstrates the myriad of problems encountered, and the general lack of success in establishing therapeutic methods based on heterologous expression of proteins, which problems are due in large part to the absence of reliable promoter constructs capable of providing expression adequate for therapeutic application.

Next, Applicant asserts that because the specification teaches how to prepare microencapsulated cells comprising a nitric oxide synthase under the control of a tetracycline- or ecdysone-inducible promoter and teaches that the microcapsules can be used in therapy the skilled artisan is provide with information to make and use the claimed microcapsules and to use the microcapsules in therapy. This argument is not persuasive because the statute requires that

the statute requires that the specification disclose "the manner and process of making and using it [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same". In an unpredictable art, it is not sufficient to teach how to make a product and assert that it can be used in therapy without teaching how to use the invention (*i.e.*, the manner and process of using it). In the instant case, the skilled artisan would not know how to obtain a therapeutic effect using the invention.

Applicant provides a quotation from *In re Wright* (CA FC) 27 USPQ2d 1510 which states, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)." Applicant urges that the instant disclosure not only broad terminology which is readily understandable to one of ordinary skill in the art, but also illustrative examples of the treatment of cancer using the claimed microcapsules.

This argument has been fully considered but is not deemed persuasive. The Court's position as stated in the passage cited by Applicant is clarified in the sentence that immediately follows it, which states, "[w]hen rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to

provide suitable proofs indicating that the specification is indeed enabling. *Marzocchi*, 439 F.2d at 223-24, 169 USPQ at 369-70" (page 1513). Thus, the Court is not suggesting that the provision of broad terminology is always sufficient to enable a claim, as Applicant appears to be insinuating. Instead, the court is merely stating the fact that the PTO bears the initial burden of establishing why the broad terminology or other teachings set forth in the specification fail to enable the claims. In the instant case, the Office has clearly set forth the reasons why the skilled artisan would not know how to use the claimed invention. With regard to the illustrative examples of the treatment of cancer using the claimed microcapsules cited by Applicant, as discussed on page 16 of the previous Office Action, the admixture of dispersed tumor cells with dispersed microencapsulated cells as provided in Example 6 clearly fails to model the complexity of a tumor *in situ*, and given the general failure of xenograft tumor models of cancer to predict clinical efficacy of cancer treatments, the clinical outcome of administering the encapsulated cells to a cancer patient remains highly unpredictable. Thus, the skilled artisan seeking to use the microencapsulated cells of the invention to treat cancer would clearly have to engage in undue experimentation to establish a clinically efficacious treatment.

Finally, Applicant asserts that the fact that some experimentation may be employed does not make the amount of experimentation undue if a person of skill in the art typically engages in such experimentation and requiring Applicant's to provide an exhaustive experimental study into any and all possible embodiments would discourage disclosure of discoveries.

These arguments are not deemed persuasive because requiring that the disclosure teach the skilled artisan how to use the claimed invention without undue experimentation is clearly consistent with the principles underlying 35 USC §112 and, with regard to the legal standard for

"undue experimentation", *In re Wands* is clear, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* ...They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims" (8 USPQ2d 1400, page 1404). The present arguments appear to be Applicant's opinion of what is routine experimentation and not the legal analysis set forth in *In re Wands*. In contrast, analysis of the instant claims according to the "Forman factors" is clearly set forth in the previous Office Action and the arguments provided by Applicant to rebut the prima facie case has been found unpersuasive for the reasons set forth herein above.

Applicant's arguments have been fully considered but are not deemed persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER